

History of X-Ray Crystallography^a

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Abstract

A brief account is given of the history of X-ray crystallography from its beginning in 1912 to the present time. Particular emphasis is placed on the phase problem, the major obstacle in the path leading from the observed X-ray diffraction pattern to the desired crystal structure. The essential role which mathematics plays in resolving this problem is also stressed.

In this brief sketch of the history of X-ray crystallography, I would like to emphasize the important role played by the development of the direct methods which were devised to solve the central problem of X-ray crystallography, the so-called phase problem. I shall also stress the importance of cross disciplinary research, in particular the essential role which mathematics played in this development.

In 1895 Wilhelm Röntgen discovered X-rays. With this discovery, the stage was set for the creation of the modern science of X-ray crystallography.

In 1912 Paul Ewald was completing his doctoral dissertation about the optical properties of a medium consisting of a regular arrangement of isotropic resonators. A crystalline solid which, on the sub-microscopic level, consists of a triply periodic, regular arrangement of atoms, or molecules, is therefore precisely the kind of medium with which Ewald was concerned. Since the smallest interatomic distances in a crystal are of the same order of magnitude as the wavelengths of X-rays, it occurred to Max von Laue, upon learning of Ewald's results, that a crystal might serve as a three-dimensional diffraction grating for X-rays. In order to test this hypothesis, he prevailed upon the younger physicists Walter Friedrich and Paul Knipping to perform the necessary scattering experiment.

The scattering experiment indeed showed that when a beam of X-rays strikes a crystal, the crystal scatters the incident beam in many different directions and with different intensities. If these scattered X-rays strike a photographic plate they will blacken the plate at those points where the scattered rays strike the plate. In this way one obtains the so-called diffraction pattern. This experiment marked the birth of the science of X-ray crystallography and, because of its fundamental importance in determining crystal and molecular structures, must be regarded as a landmark event in twentieth century science. The major obstacle in the path leading from the observed diffraction pattern to the desired crystal structure is known as the phase problem, for reasons to be given shortly. I propose to give here a brief historical account of the methods devised to overcome this obstacle, the so-called direct methods of X-ray crystallography.

It has already been remarked that a crystal may be regarded as a regular triply periodic arrangement of an array of atoms. One imagines three families of planes, the planes in each family being parallel to and equidistant from one another. In this way, one obtains a tiling of the crystal space by means of congruent parallelepipeds, each one of which is said to be a fundamental parallelepiped, or unit cell, of the crystal.

If each unit cell contains a molecule—a collection of atoms—in its interior, and if the atoms are arranged in precisely the same way in all the unit cells, then each unit cell and its contents are indistinguishable from every other unit cell and its contents.

There corresponds to each atom an electron density function; hence, by superposition of the individual atomic

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electron density functions, one obtains an overall electron density function $\rho(\mathbf{r})$, a nonnegative function of the position vector \mathbf{r} which gives the number of electrons per unit volume at the position \mathbf{r} . It is clear from the geometric construction that the electron density function in any unit cell is identical to that in every other unit cell. Hence $\rho(\mathbf{r})$ is a triply periodic function of position, and this property may be taken as the mathematical definition of a crystal.

If on the other hand we choose to regard a crystal as a triply periodic arrangement of an array of atoms, or molecules, then by a crystal structure we mean simply the arrangement and identities of the atoms in the unit cell and by a molecular structure the arrangement and identities of the atoms in the molecule.

It was recognized almost from the beginning that the diffraction pattern, the directions and intensities of the X-rays scattered by a crystal, is uniquely determined by the crystal structure; which is to say that if one knew the crystal structure—the arrangement of the atoms in the crystal—then one could calculate the diffraction pattern completely. It turns out that, conversely, diffraction patterns determine, in general, unique crystal and molecular structures, although this fact was not known until many years later. In short, the information content of a typical molecular structure coincides precisely with the information content of its diffraction pattern. It is a measure of the great advances made by the new science of X-ray crystallography that, nowadays, one can routinely transform the information content of a diffraction pattern into a molecular structure, at least for the so-called “small” molecules, that is those consisting of some 150 or fewer non-hydrogen atoms.

Since X-rays, like ordinary visible light, are electromagnetic waves, they have a phase as well as an intensity, just as any other wave disturbance. In order to work backwards, from diffraction patterns to crystal and molecular structures, it turns out to be necessary to measure not only the intensities of the X-rays scattered by the crystal but their phases as well. However, the phases cannot be measured in the ordinary kind of diffraction experiment; they appear to be irretrievably lost. Only the intensities can be directly measured. This then gives rise to the central problem of X-ray crystallography, the so-called phase problem, how to deduce the values of the phases of the X-rays scattered by a crystal when only their intensities are known. For some 40 years after the landmark experiment of Friedrich and Knipping, all attempts to find a general method for going directly from the diffraction pattern, that is measured intensities alone, to the crystal structure, with or without the intervention of the phases (a method that would be useful for the complex structures of interest to chemists, biologists, and mineralogists) were defeated.

Because the needed phase information was lost in the diffraction experiment, it was thought that one could use arbitrary values for the phases associated with the measured

intensities of the scattered X-rays. In this way one obtains a myriad of different crystal structures, all consistent with the known intensities. It therefore came to be generally believed that a procedure for going directly from the measured intensities to crystal structures could not, even in principle, be devised. By the same thinking, the problem of deducing the values of the individual phases from the diffraction intensities, the so-called phase problem, was also thought to be unsolvable, even in principle. It wasn't until the early 1950s, through the exploitation of special properties of molecular structures and through a simple mathematical argument, that these erroneous conclusions were finally refuted.

The special property that all crystal and molecular structures possess may be summed up in one word: atomicity. Thus the electron density function $\rho(\mathbf{r})$ in a crystal takes on large positive values at the atomic position vectors and drops to small values between the atoms. If our goal is merely to determine the positions of the atoms—the positions of the maxima of $\rho(\mathbf{r})$ —rather than the much more complicated electron density function associated with the distribution of atoms in the crystal, then our problem is greatly simplified; it turns out to be not only determinate but actually greatly overdetermined by the available X-ray diffraction intensities.

This is most easily seen by eliminating the lost phase information from the relationships between the diffraction pattern and the crystal structure. Doing this results in a system of equations relating the diffraction intensities alone with the atomic position vectors. Because the number of these relationships far exceeds (by a factor of ten or so) the number of unknown position vectors needed to define the crystal structure, our problem is greatly overdetermined. Thus it is clear that there exist relationships between the measured diffraction intensities and the lost phases that may be exploited. It follows that the phases of the scattered X-rays are also determined by their intensities. In short, the lost phase information is to be found among the available intensities, and the phase problem is therefore a solvable one, at least in principle. There remains the task of devising numerical algorithms leading from the abundance of experimentally measured diffraction intensities to the values of the individual phases. The techniques of X-ray crystallography that deduce the individual phases by exploiting relationships between measured diffraction intensities and phases are known as direct methods.

The argument just presented was in fact anticipated in 1927 by Heinrich Ott [1], who showed by algebraic analysis and applications that the method is capable of solving simple centrosymmetric structures, in which all phases must be either 0 or π . The method was further elaborated by Kedaraswar Banerjee in 1933 [2] and Melvin Avrami in 1938 [3] but was clearly of only limited value in applications. While this early work of Ott, Banerjee and Avrami shed important light on the more general phase problem, it

attracted little attention at the time and was not further developed; it appears now to be all but forgotten.

My work on this problem started in 1948 about a year after I joined the Naval Research Laboratory in Washington, D.C. and initiated my collaboration with Jerome Karle. It had been some 35 years since Friedrich and Knipping had carried out their famous experiment, and by 1947 the phase problem, the central problem of X-ray crystallography, was still unsolved and generally regarded as unsolvable. The central importance of this problem and its strong mathematical component combined to provide a challenge that could not be denied.

Then too, there was a certain air of mystery surrounding the problem. On the one hand the simplicity and logic of the argument “proving” its unsolvability, even in principle, appeared to be overwhelming. On the other hand, crystal and molecular structures were being solved, although the structures studied were almost always very simple ones involving a small number of atoms or larger structures containing one or a small number of heavy atoms, for which special techniques had been devised. It had not yet been generally understood that the implicit assumption of atomicity and the concomitant trial-and-error approach to most structure solutions had imposed a powerful restriction on the permitted values of the phases.

The first important contribution that Karle and I made was the recognition that it would be necessary to exploit prior structural knowledge to transform the phase problem from an unsolvable one to one that was solvable, at least in principle. Our first step in this direction was to exploit the nonnegativity of the electron density function $\rho(\mathbf{r})$. Before our analysis was complete, however, David Harker and John Kasper published their famous paper [4] in which they derived inequalities in which the measured intensities restrict the possible values of the phases. This was a very mysterious paper, because nowhere in it does there appear any explicit mention of the basis for the inequality relations, and indeed the most important fact is conspicuous by its absence. It is simply that the electron density function is nonnegative everywhere. This fact is, however, implicit in Harker and Kasper’s work. In very short order Karle and I completed our own analysis and derived the complete set of inequality relationships based on the nonnegativity of the electron density function [5]. It includes the Harker-Kasper inequalities as a special case, and many others besides. Although the complete set of inequalities greatly restricts the values of the phases, the relations appear to be too intractable to be useful in applications, except for the simplest structures, and their potential has never been fully exploited.

The recognition in 1950 and 1951 that molecules consist of atoms that, to a good approximation, may be regarded as points transformed completely the nature of the phase problem. While it meant accepting as fact that the observed dif-

fraction intensities by themselves were indeed not sufficient to determine a unique electron density function, it also meant that they were more than sufficient, by far, to determine the atomic position vectors [6]. It meant as well that the phases corresponding to the point atom structure were greatly overdetermined by the available intensities. Finally, it meant that a formidable psychological barrier had been removed, because it now made sense to look for a solution to the phase problem, for numerical algorithms leading from measured intensities to individual phases. In hindsight it is perfectly clear that owing to the great overabundance of diffraction data, a probabilistic approach is called for; some 40 years ago, however, this was not so apparent.

Before we could even get started, an unexpected complication arose. It turned out that because the values of the individual phases clearly depend not only on the crystal structure but also on the choice of origin, they are not uniquely determined by the crystal structure alone. It followed that the diffraction intensities alone do not determine unique values for the phases. The process leading from diffraction intensities to phases would have to include a recipe for specifying the origin. This required that we separate out two contributions to a phase, one due to the crystal structure alone and one due to the choice of origin. We clearly needed to study how a phase is transformed when the origin is shifted, a problem that was complicated by the fact that the permissible origins depend on the crystallographic elements of symmetry, which were usually known in advance.

The solution was made easier by the discovery that there are always certain linear combinations of the phases, the so-called structure invariants, that are uniquely determined by the crystal structure alone and are independent of the choice of origin. It is therefore only the values of the structure invariants that we can hope to estimate from the measured intensities. Once we have estimated a sufficient number of these we can then hope to evaluate the individual phases by a process that incorporates a recipe for specifying the origin.

What was clearly called for was devising a method for identifying the structure invariants, and then using these to come up with recipes for fixing the origin appropriate to the different elements of crystallographic symmetry that may be present. Once this was done there would remain the task of estimating the values of the structure invariants by means of their conditional probability distributions, assuming that an appropriately chosen set of diffraction intensities is known.

Beyond any doubt our most important contribution during the early 1950s was the introduction of probabilistic techniques—in particular, use of the joint probability distribution of several diffraction intensities and the corresponding phases—as the central tool in the solution of the phase problem [7]. We assumed to begin with that all positions of the atoms in the unit cell of the crystal were equally likely, or, in the language of mathematical probability, that the atomic

position vectors were random variables, uniformly and independently distributed. With this assumption the intensities and phases of the scattered X-rays, as functions of the atomic position vectors, are also random variables, and one can use the methods of modern mathematical probability theory to calculate the joint probability distribution of any collection of intensities and phases. A suitably chosen joint probability distribution leads directly to the conditional probability distribution of a specified structure invariant, assuming again an appropriately chosen set of diffraction intensities. The conditional distribution in turn leads to the structure invariant, an estimate of which is given, for example, by its most probable value. Once one has a sufficiently large number of sufficiently reliable estimates of structure invariants, one can use standard techniques to calculate the values of the individual phases, provided that the process incorporates a recipe for specifying the origin.

Although probabilistic methods played an essential role in the development of the direct method and provided it with its logical foundation, it must also be pointed out that non-probabilistic methods also played an important part. In this connection the early work of Sayre [8], Zachariasen [9], Cochran [10] and Woolfson [11] should be mentioned. In particular the well known Sayre equation, a relationship of fundamental importance among measured magnitudes and unknown phases, continues to be useful to the present day and lies at the heart of some of the more successful computer programs for solving crystal structures.

I cannot conclude this brief account of the early history of the direct methods of X-ray crystallography without also describing the reception this work received at the hands of the crystallographic community. This was, simply, extreme skepticism, if not outright hostility. In hindsight I think this reaction was due, first, to the strong mathematical flavor of this early work, not well understood by most crystallographers, as well as the ingrained and almost universal belief that the phase problem was unsolvable in principle and that any claim to the contrary must therefore be flawed. This nearly universal skepticism and inability to understand the

proposed solution no doubt explains why so few early attempts to apply the new methods were made. It wasn't until the 1960s when easy to use computer programs became available that widespread applications were made.

Today some 100,000 molecular structures are known, most determined by the direct methods, and about 5,000 new structures are added to the list every year. It is no exaggeration to say that modern structural chemistry owes its existence to this development.

Although no equations are shown in this article, it should be clear that the developments described here would not have been possible without strong dependence on mathematical techniques, in particular the modern theory of mathematical probability, and it is this interaction between mathematics and the phase problem of X-ray crystallography which I have tried to emphasize in this article. Work on the phase problem continues to this day and applications to structures of ever increasing complexity continue to be made. It still appears that progress is made only in proportion to our ability to bring more powerful mathematical techniques to bear on this fascinating problem.

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